

Maleic Hydrazide
Position Document 1

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Maleic Hydrazide: Position Document 1

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CONTENTS

I. Background

- A. General Chemistry
- B. Physical Characteristics
- C. Environmental Characteristics
- D. Metabolism
- E. Monitoring
- F. Residues
 - (1) Potatoes and Onions
 - (2) Tobacco
 - (3) Meat, Milk, Poultry, and Eggs
- G. Production
- H. Registered Uses and Supply
 - (1) Products
 - (2) Use Patterns
 - (3) Tolerances
- I. Human Exposure

II. Regulatory History

- A. Registrations and Tolerances
- B. Investigations of Adverse Effects
- C. Pesticide Episode Response Branch Report
- D. Referral to Office of Special Pesticide Reviews

**III. Summary of Scientific Evidence to Support
Rebuttable Presumption: Chronic Toxicity**

A. Oncogenic Effects in Test Animals

- (1) Mouse Studies
- (2) Rat Studies
- (3) Conclusion

B. Mutagenic Effects

- (1) Chromosomal Mutations
- (2) Gene Mutations
- (3) Other Tests Bearing on Mutagenicity
- (4) Conclusion

C. Reproductive Effects in Animal Species

- (1) Nonmammalian Studies
- (2) Mammalian Studies
- (3) Conclusion

IV. Other Studies

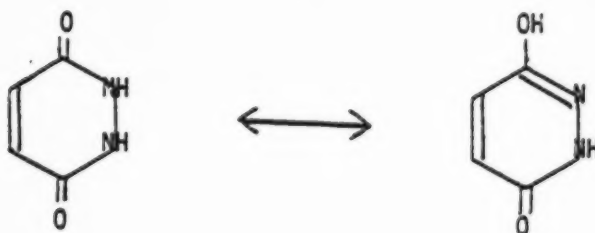
- (1) Formation of N-nitroso Compounds

List of Appendices

I. Background

A. General Chemistry

Maleic hydrazide or MH [1,2-dihydro-6-pyridazine 3,6-dione (Structure A) or 6-hydroxy-3(2H)-pyridazinone (Structure B)] is a plant-growth regulator in the heterocyclic class of pesticides. MH has an empirical formula of $C_6H_4N_2O_2$ and a molecular weight of 112.09. Its structural formulae are:



Structure A

Structure B

MH is slightly acidic and may be titrated as a monobasic acid. It forms salts with diethanolamine (DEA), triethanolamine, and alkalies; but it is stable in acidic and basic solutions. The 6-hydroxy-3 (2H)-pyridazinone isomer can exhibit phenolic properties under physiological conditions.

B. Physical Characteristics

MH is an odorless white crystalline powder. It melts at 296° to 298°C and decomposes above 300°C. It is not decomposed by ultraviolet radiation. MH is soluble in water at concentrations as great as .4g/100 ml at 20°C. MH is also soluble in alkaline solutions. The sodium, potassium, and diethanolamine (DEA) salts are soluble in water and hot alcohol. The solubility of MH in other solvents at 25°C is shown in Table 1.

Table 1. Solubility of MH.

Solvent	Solubility (ppm)
Acetone	1,000
Ethyl alcohol	1,000
Dimethyl formamide	20,400
Dimethyl sulfoxide	90,000
Xylene	<1,000

MH has no vapor pressure at room temperature.

C. Environmental Characteristics

The Ecological Monitoring Branch (EMB) of the Technical Services Division within the Office of Pesticide Programs is not currently monitoring for MH in human tissues, agricultural or urban soil, air, or estuarine and ocean organisms (1).

We have seen no evidence that MH persists in water, although it may occur there as a result of runoff. Since MH is not volatile, it is not found in air. Levi and Crafts studied the persistence of MH in heavily treated soils by measuring plant growth in successive harvests (2). The half-life of MH in soil treated with MH in concentrations of 1 to 4 ppm is 40, 7, and 4 days in clay, sand, and muck soils, respectively (3).

The effects of MH on soil bacteria, fungi, and plant pathogens have been extensively researched. In most cases MH slightly inhibits soil bacteria, but it can stimulate soil microflora and fertilize soils. The effects on fungi range from inhibition to stimulation; in some cases MH has no effect. Stimulation occurs indirectly because MH degradation products may be used as a nitrogen source. The fact that no effect is sometimes seen may result from the competition of inhibitory and stimulating effects. Generally, microorganisms in the soil rapidly degrade MH (4). We have seen no reports of other data on environmental chemistry.

D. Metabolism

MH, which is generally translocated from the treated leaves down into the rest of the plant, is relatively stable. Residues occur in potatoes and roots of turf grasses as long as 8 months after treatment (5).

Despite substantial research, the mechanisms of MH metabolism in plants and animals are not well known. Initially, MH was thought to degrade to either maleic or fumaric diamide, which might yield the ammonium salts of the corresponding acids on hydrolysis (6). Towers later concluded that MH in leaf segments of wheat becomes detoxified by the formation of a glycoside (7).

When ^{14}C -MH was applied to specific leafy plants, it migrated from the phloem to the xylem; and mature leaves above the treated leaf became radioactively labelled. Extracts of young wheat seedlings treated with ^{14}C -MH exhibited two radioactive spots on chromatograms and autoradiograms. One spot contained 15% of the total radioactivity and was identified and confirmed as the beta-glycoside of MH (7, 8). MH also forms complexes in other plants (9).

There is no clearly documented evidence that hydrazine, a known carcinogen (10), is a metabolite of MH.

Biswas and co-workers (11) postulated that when ^{14}C -MH was applied to tea plants it was degraded to lactic acid, succinic acid, maleamide, and hydrazine. However, their data were inadequate to support this conclusion.

Rates of MH absorption vary only moderately among plant species (12). The tomato plant was selected in studies of the effects of plant turgidity, application rate, temperature, light, humidity, and formulation on MH absorption. Tests with alkali salts, volatile amines, and nonvolatile amines of MH showed that the nonvolatile amine salts, such as the DEA salt, were absorbed to the greatest extent, followed by the potassium salt to which sorbitol was added in the formulation (12).

Recently, it was reported that tobacco treated with the DEA salt of MH contained as much as 173 ng of N-nitrosodiethanolamine per gram of tobacco, whereas tobacco treated with the potassium salt of MH contained only 0.1 ng of N-nitrosodiethanolamine per gram of tobacco (13). This finding indicates that DEA may have been the source of N-nitrosodiethanolamine, which is reported to be oncogenic (14).

MH binds in vitro with ribonucleic acid and with proteins such as egg albumin, zein, and hexokinase. Stronger

bonds are formed and more MH is bound by the diethanolamine salt of MH than by the potassium salt of MH (9).

When ^{14}C -MH was administered to rats in a single oral dose, they excreted 77 and 12% of the compound in urine and feces, respectively, in 6 days. The products excreted in urine were MH (92 to 94%) and a conjugate of MH (6 to 98%). Only trace amounts of MH (<0.001%) were detected in tissues or blood samples after 3 days. Only 0.2% of the radioactive MH was excreted through the lungs (15).

El Masri (16) administered single oral doses of MH to rabbits. About 60% of the dose was excreted unchanged in the urine. Neither hydrazine, conjugated glucuronic acid, nor ethereal sulfate was excreted.

Barnes and co-workers (17), in a study that substantiates that of El Masri, administered oral doses of MH (100 mg/kg) to rabbits. From 43 to 62% of the dose was excreted within 48 hours. The authors did not describe the mode of excretion. Similar results were obtained with a 2-g dose. No glucuronides or ethereal sulfates were detected. The authors speculated that the 40% of MH which could not be accounted for may have been more slowly excreted or broken down (17).

E. Monitoring

The Market Basket Survey of the Food and Drug Administration (FDA), which monitors pesticide residues in a sample daily diet of an average 16- to 19-year-old American male in various regions of the country, has not analyzed foods for MH. An FDA official stated in 1974 that "FDA cannot justify surveillance for MH because practical resource constraints, relative risks and the myriad of possible pesticide/food combinations force FDA to make a careful choice of the pesticides and foods which are included in its pesticide program" FDA further stated that it "will seriously consider including MH in the pesticide program if EPA concludes that the toxicity of MH is of such magnitude that periodic testing is needed to protect public health" (18). The MH Working Group knows of no other Federal program to monitor MH.

F. Residues

(1) Potatoes and Onions

Uniroyal Chemical, one of the primary producers of technical grade MH, has provided EPA with monitoring data on the MH residues in potatoes and onions harvested from 1969 through 1973 (19). The residue data reported for potatoes and onions were within the established tolerance limits (50 ppm and 15 ppm, respectively) when MH-30 (58% DEA salt of MH in an inert vehicle) was applied according to label directions (19).

(2) Tobacco

Tobacco and cigarettes analyzed for MH residues after the 1970 growing season contained residues of 19 to 31 ppm and 18 to 30 ppm, respectively (20). The Department of Agriculture found average residues of 50 to 100 ppm on tobacco, although in rare cases MH residues exceeded 500 ppm (21).

(3) Meat, Milk, Poultry, and Eggs

Dehydrated potato tubers used as feed for beef and dairy cattle, swine, lambs, horses, and poultry can make up 7 to 50% of the animal's diet, depending on the animal. If it is assumed that there is no loss of maleic hydrazide in the dehydration process, quantities of MH as low as 15 ppm or as high as 90 ppm could appear in the diets of turkeys or broilers and beef cattle, respectively (12).

The Chemistry Branch of the Registration Division of EPA is not aware of any metabolic studies on large animals or of feeding studies on livestock or poultry (12). Therefore, we are unable to assess the potential for the appearance of secondary residues of MH in meat, milk, poultry, and eggs.

G. Production

Section 7(c) of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) requires manufacturers and

formulators to submit information on production, distribution, and sales of MH and its formulations to EPA. Under Sections 7(d) and 10 of FIFRA, this information may not be made available to the public. The information is available to the Administrator in a confidential appendix to this report (22).

H. Registered Uses and Supply

(1) Products

The diethanolamine salt of MH is registered for use on tobacco, potatoes, onions, and nonbearing citrus trees; it is also registered for use on commercial turf areas that are difficult to mow and not used for grazing, such as grass along highways, airport properties, industrial areas, and golf course roughs. The potassium salt is registered only for use on tobacco.

Table 2. MH Pesticide Registrations.

Compound	Federal		Applicants for Federal Registrations under 40 CFR 162.17	
	Registrants	Products	Registrants	Products
Maleic hydrazide	5	6	3	3
Diethanolamine salt of MH	42	57	-	-
Potassium salt of MH	5	10	1	1

(2) Interruptions

According to the Government Accounting Office (GAO) report (18), MH formulations are principally used to prevent suckers on tobacco. It is estimated that about 4% of the U.S. tobacco crop acreage is treated with the DEA of MH and 45% is treated with the potassium salt formula. Its second greatest use on crops is in the prevention of harvest sprouting of potatoes and onions. MH is also used to retard grass growth along highways.

When data on agricultural applications provided by § (1) show that the use of MH per acre may have decreased (Table 3).

Fiscal	Si	Sites Reporting	Average Total
Year	Reps (number)	Application (number)	(pounds/acre)
1969	1,6	7	1.43
1970	1,3	3	1.80
1972	1,4	3	3.00
1973	1,4	5	2.25
1974	1,1	2	1.25

Tolerances

1 tolerance of 50 ppm in potatoes and 15 ppm in onions (FR 180.175), and a tolerance of 160 ppm for MH as a pesticide in potato chips (21 CFR Section

123.270) have been established. The establishment of tolerances for MH on various foods, particularly potatoes and onions, was necessary because MH is translocated into these foods before harvest. These residues cannot be removed after harvest by washing or any other process.

The World Health Organization (WHO) and the Food and Agricultural Organization (FAO) of the United Nations have not set an acceptable daily intake (ADI) for MH. The ADI is a dosage which, if ingested daily for the lifetime of an individual, is assumed to cause no appreciable risk. No ADI data have been found in EPA files.

I. Human Exposure

Humans are most likely to be exposed to maleic hydrazide in treated potatoes and onions, which are consumed at the rate of 119 and 12.5 pounds per person per year, respectively (23). However, all potatoes and onions may not be treated with MH, and there are no figures available that show the percentages of potatoes and onions that are treated with MH. Users of smoking or chewing tobacco would be further exposed to MH (13).

II. Regulatory History

A. Registration and Tolerances

MH was originally synthesized in 1895, but its ability to regulate plant growth was not discovered until

1949, when Schoene and Hoffman (24) reported that MH has a pronounced, although temporary, inhibitory effect on plant growth, but causes little apparent damage to the plants.

On July 13, 1955, Uniroyal (then the United States Rubber Company) petitioned FDA to establish tolerances for MH on potatoes, onions, and tobacco of 20, 10, and 10 ppm, respectively. However, this petition was not accepted under Section 408 of the Federal Food Drug and Cosmetic Act (FFDCA), because FDA did not think that the use of MH on onions and potatoes to prevent sprouting fit the definition of an economic poison, as defined in FIFRA. Uniroyal requested a public hearing under Section 701(e) of FFDCA to determine if MH was an economic poison. A new petition, submitted October 28, 1956, proposed tolerances of 30, 15, and 75 ppm for potatoes, onions, and potato chips, respectively; it was denied because Uniroyal failed to show that MH was required in the production of potatoes and onions. Tobacco was not included, because it is not regulated under FFDCA. In 1960, in response to another petition submitted April 30, 1959, tolerances of 50, 15, and 160 ppm on potatoes, onions, and potato chips, respectively, were established under the amended FFDCA.

A petition submitted December 10, 1960, by Uniroyal to establish MH tolerances on lemons, peaches, and cranberries of 5, 15, and 20 ppm, respectively, and a petition

filed on June 10, 1962, requesting a tolerance of 20 ppm on cranberries were withdrawn because Uniroyal could not provide enough data to support the petitions.

The products containing sodium salt of MH were registered from 1952 through 1967. The registrant, Uniroyal Chemical, did not apply for reregistration. The first registrations of the products containing the DEA and the potassium salts of MH were issued in 1952 and 1969 respectively.

B. Investigations of Adverse Effects

The suspicion that MH may have adverse effects on animals first arose in 1951 when it was claimed that MH is toxic to and retards the growth of frog, toad, and salamander larvae (25).

Between 1951 and 1969 several studies appeared relating MH to oncogenicity, mutagenicity, and reproductive effects. These studies were closely watched by the Agriculture Research Service (ARS), USDA. A major source of concern was a study by Dickens and Jones (26) linking MH to oncogenicity. In response to Dickens and Jones' study, meetings were held October 6 and 7, 1965, to discuss whether MH is oncogenic. The scientists present concluded that MH was only suspect and that more studies with larger numbers and

different species of animals were needed (27). Furthermore, both oil and aqueous solutions of MH were used in the studies by Dickens and Jones, and they did not use a control group. In an FDA conference on MH held on October 14, 1965, it was decided that the results reported by Dickens and Jones had no relevance to the safety of MH as a food additive (28).

Although Epstein's research (29) showing that tumors were induced in an area other than the site of injection indicated that MH is carcinogenic, USDA took no regulatory action (30) because FDA did not consider the route of administration in these studies appropriate (31). However, the Director of ARS later requested cancellation of the registration of MH-30 (DEA-MH formulation) because another pesticide had been cancelled on the basis of results of studies in which it was administered parenterally (32). However, no regulatory actions were taken on registrations of products containing MH.

On July 13, 1973, The Honorable Julia Butler Hansen, House of Representatives, requested GAO to provide her with information on Federal testing of MH. The GAO report on MH, published October 23, 1974, reviewed the published scientific findings related to the adverse effects and described three hazards believed to be associated with MH: carcinogenicity, mutagenicity, and reproductive effects

(18). GAO recommended that additional testing and research be carried out on MH to determine if it adversely affects humans or the environment. GAO also recommended that FDA periodically test potatoes and onions to make sure that the residues are within the established tolerances (18). Since publication of the GAO report, several more studies of the possible adverse effects of MH on animals have been published.

The 1969 HEW Mrak Report listed MH as a possible oncogenic agent but did not conclude that it was oncogenic (33). MH was among the 120 compounds tested earlier for tumorigenicity by the National Cancer Institute, but it was not found to be carcinogenic (34). More recently, MH was listed as a suspected carcinogen by the Department of Health, Education, and Welfare (35).

C. Pesticide Episode Response Branch Report

Sixteen episodes involving MH have been reported to EPA, two of which were solely related to MH. In the other episodes MH had been used in combination with other pesticides. The Pesticide Episode Response Branch, EPA, stated that there is no significant history of accidents associated with MH and that it appears inappropriate to identify MH as the active agent in these poisonings (36).

D. Referral to the Office of Special Pesticide Reviews

MH was referred to OSPR because data indicated that MH may be linked to oncogenic, mutagenic, and reproductive effects.

III. Summary of Scientific Evidence to Support a Rebuttable Presumption: Chronic Toxicity

A. Oncogenic Effects in Test Animals

40 CFR Section 162.11 (a)(3)(ii)(A) provides that "a rebuttable presumption shall arise if a pesticide's ingredient(s)...induces oncogenic effects in experimental mammalian species or in man as a result of oral, inhalation, or dermal exposure...." Section 162.3(bb) defines the term oncogenic as "the property of a substance or a mixture of substances to produce or induce benign or malignant tumor formation in living animals."

There are a number of studies on MH's oncogenic properties cited in the literature. MH, either as the sodium or potassium salt or as the DEA salt has been applied to rats or mice by injection and by dermal and oral administration. This Agency's Carcinogen Assessment Group (CAG) has evaluated these studies and concluded that MH possesses oncogenic potential. The Working Group concurs with CAG's position. CAG's evaluation of the carcinogenicity of Maleic Hydrazide (37) is summarized below.

(1) Mouse Studies

Epstein and co-workers (29) found evidence of excess tumor induction in male but not female mice. Their study showed a statistically significant increase of liver tumors (hepatomas) in males injected subcutaneously with 0.1, 0.1, 0.2, and 0.2 ml containing 5, 10, 20 and 20 mg of MH suspended in tricaprylin 1, 7, 14, and 21 days after birth, respectively. After 49 weeks, 4 of the 48 survivors in the control group had hepatic tumors compared to 17 of the 26 survivors in the experimental group.

In a second study, Barnes and co-workers (17) found a statistically significant increase in the total number of tumors, including benign tumors, in female mice fed 1% sodium salt of MH (Na-MH) in the diet for 100 weeks. The incidence of tumors in the experimental population (7/8) was significantly higher than that in the control group (0/4) at a p-level equal to 0.01. Tumor incidences in control and experimental male populations were not statistically different.

In the same study, the number of skin tumors in mice to which MH and croton oil were simultaneously applied was not greater than that in mice treated with only croton oil. Furthermore, implantation of cholesterol pellets containing 20% MH in the bladders of mice did not cause any increase in the incidence of tumors in the mice that survived treatment (17).

Innes and co-workers (34) carried out feeding studies on mice for approximately 18 months. Upon completion of these studies, the authors concluded that MH did not cause a significant increase in tumors.

Mukhorina (38) injected one group of mice with the DEA salt of MH (DEA-MH) and fed a second group a diet containing DEA-MH. In neither group was the incidence of tumors significantly above that in control groups.

(2) Rat Studies

Six 100-g rats were injected subcutaneously with 2 mg of MH per rat twice weekly for 65 weeks (26). Transplantable sarcomas developed at the site of injection in three of the six experimental animals. None of the six control rats had tumors. As judged by the authors, the study demonstrated that MH is oncogenic; however, the p-value of 0.091 is not significant.

In studies by Barnes and co-workers (17), who administered MH orally and by injection and studies by Hunter and co-workers (39), in which MH and DEA-MH salt were administered by injection, MH did not cause a statistically significant increase in tumor incidence. Data from other studies (40,41,42) were found to be inadequate (37, 43), and no conclusions should be drawn from them.

(3) Conclusion

The Working Group has concluded from the studies described above that MH is oncogenic in mice. Consequently, the Working Group recommends that a rebuttable presumption be issued on pesticides containing MH pursuant to Section 162.11 (a)(3)(ii)(A).

B. Mutagenic Effects

40 CFR Section 162.11 (a)(3)(ii)(A) provides that a rebuttable presumption shall arise if a pesticide's ingredient(s), metabolite(s), or degradation product(s) induce mutagenic effects, as determined by multitest evidence. Section 162.3 (y) defines the term "mutagenic" as "the property of a substance or mixture of substances to induce changes in the genetic complements of either somatic or germinal tissue in subsequent generations."

This review of the studies is divided into three sections: chromosomal mutations, gene mutations, and other tests bearing on mutagenicity. These studies were evaluated by the Health Effects Research Laboratories (HERL) (44).

(1) Chromosomal Mutations

Maleic hydrazide breaks chromosomes of a number of plant species, producing deletions, duplications,

and chromosomal rearrangements. The effect is dependent on the stage of the cell cycle, and occurs during the G_1 through S phases (45).

Manna and Parida (46) examined meiotic chromosomes from several grasshopper species which were given MH in food. The mortality rate 48 hours after feeding ranged from 17 to 58%, depending on the species; none of the controls died. In treated males chromatid and chromosome breaks were noted at various stages of meiosis; chromosome bridges and lagging chromosomes were seen in anaphase I and II figures; and chromosome stickiness was prevalent in all meiotic stages examined. In control males, no breaks were found, and chromosome stickiness was much less than in treated animals.

Manna and co-workers (47) injected mice with MH (167 mg/kg body weight^{1/}) and then examined their bone marrow for chromosome aberrations 10 to 120 hours after treatment. The frequency of gaps, chromatid breaks, and translocations significantly increased in treated animals. An increase in

^{1/}The LD₅₀ for MH injected subcutaneously in mice is 8800 mg/kg; that for MH injected subcutaneously in rats is 1300 mg/kg. The LD₅₀ for MH administered orally in rats is 3800 mg/kg (36).

isochromatid breaks was not noted, a fact which may indicate that MH does not affect cells in the G_1 phase of the cell cycle. Another investigator has claimed that breaks are produced by MH in cultured mouse fibroblasts (48). Chromosome aberrations did not increase in liver cells of rats fed 1% MH in the diet (49). However, the frequency of mitotic cells in adult rat liver is very low. Na-MH does not inhibit mitosis in rats having Walker tumors (17). Results from other mammalian studies, including a dominant lethal test in mice with DEA-MH (50) have not shown increases in chromosomal aberrations.

(2) Gene Mutations

Nasrat (51) has reported that maleic hydrazide induced a significant increase ($p < .0003$) in the incidence of sex-linked recessive lethals in Drosophila melanogaster. However, there are two possible drawbacks to this study: the number of X chromosomes tested was only 1024, and the raw data are not available to rule out clustering of mutants within a few originally treated males. Clustering of mutations is probably not a problem, because the increase in mutations was noted only in the first brood which samples postmeiotic cells. Only when premeiotic stem cells are affected could multiple mutant sperm arise from a single mutant cell.

There is not much evidence that MH is mutagenic in prokaryotic systems. The Salmonella typhimurium histidine reversion test was negative both with (52) and without (53) microsomal activation. Likewise, MH was not mutagenic in Escherichia coli (54). On the other hand, in a phage-bearing strain of Bacillus megatherium MH doubled both the frequency of mutation to streptomycin resistance and the frequency with which phage entered the lytic cycle (55). MH also induced mutations in chlorophyll loci in barley (56).

(3) Other Tests Bearing on Mutagenicity

MH did not increase the frequency of sister chromatid exchanges in the chromosomes of a Chinese hamster cell line (57). It appears that in all but two mutagenicity studies MH was used and not its salts.

(4) Conclusion

Several published investigations of MH's mutagenic capacity reviewed above show that MH produces chromosome aberrations in plant and animal test systems. In addition, there is some evidence that MH induces point mutations in bacteria and plants. Accordingly, the working group recommends that a rebuttable presumption be initiated pursuant to Section 162.11(a)(3)(ii)(A).

C. Reproductive Effects in Mammalian Species

40 CFR 162.11(a)(3)(ii)(B) provides that "a rebuttable presumption shall arise if a pesticide's ingredients produces any other chronic or delayed toxic effect in test animals at any dosage up to a level, as determined by the Administrator, which is substantially higher than that to which humans can reasonably be anticipated to be exposed, taking into account ample margins of safety."

(1) Non-Mammalian Studies

Although Kang described reduced egg production and increased abnormalities in embryonic development of fresh water limpets treated with MH (58), he used dosages that were greatly in excess of those which might occur in the environment. Also, the development of a gastropod cannot be related to mammalian development in any way (59). Greulach and co-workers (25) saw no dose-related effects on embryonic growth of amphibians.

Robinson's findings (60) indicate that the reproductive system of pea aphids is adversely affected by translocated MH in bean plants. However, the reproductive system of pea aphids is different from that of humans or other mammals. Thus, these findings may not be considered relevant to mammalian reproduction (61).

Fecundity was not reduced in several generations of Drosophila melanogaster reared on a diet containing bean plants and potato tubers grown in soil treated with MH (62).

(2) Mammalian Studies

Fischnich and co-workers (63) found that fertility was disturbed in rats maintained on a diet that included tubers from potato plants sprayed with DEA-MH. However, no such effect was observed when the diet included potato tubers treated with DEA-MH after harvest. It was concluded in evaluation of this study (61,64) that the statistically weak data was inconclusive.

When sows were fed tobacco leaf extract to which MH (2 mg/kg of 58% of DEA salt) and a mixed insecticide were added, no embryonic or fetotoxic effects were observed (65). Such adverse effects were observed only when sows were fed tobacco juice and/or stake which were grown without application of any chemical, including maleic hydrazide. This study does not address the effects of translocated MH or its metabolites.

A study on reproductive effects resulting from the feeding of the Na and DEA salts of MH to rats was provided to the Agency by a registrant (41). While no significant reproductive effect can be noted for rats fed

from 0.5% to 5% Na-MH, significant differences in reproductive effects can be estimated from data provided for rats fed control diets and for rats fed the single tested dose of 0.2% DEA-MH. The fertility (pregnancies/matings), viability (pups alive at 4 days/pups born) and the lactation (pups weaned/pups alive at 4 days) are significantly reduced for DEA-MH fed rats in this study. While the average number of pups/litter for DEA-fed rats is less than half the litter size of control rats (4.3 compared to 8.8), the Working Group can not estimate from the study data whether this reduction is significant. The table below amplifies the statement above:

Table 4. Statistics on Reproductive Effects Due to DEA-MH

	Control	DEA-MH	P
1. Fertility (pregnancies/matings)	40/56	20/41	.05
2. Viability (pups alive at 4 days/ pups born)	280/333	37/73	.001
3. Lactation (pups weaned/pups alive at 4 days)	213/280	21/37	.05

From the data in this table the Working Group concludes that a daily diet containing DEA-MH causes pronounced reproductive effects in rats. Such a diet is equivalent to a daily ingestion of 100 mg/kg of DEA-MH. A comparable diet for a 60 kg man would result in a exposure

of 6000 mg/person/day. Based on the consumption figures and tolerances for DEA-MH on onions and potatoes presented earlier in this document, the average daily intake of MH in the DEA-MH formulation is calculated at 5.5 mg/person/day.

The Pesticide Chemical Review Committee (PCRC) is concerned about the proximity of the estimated exposure level (5.5 mg/day) to the observed reproductive-effect level in rats extrapolated to man (6000 mg/day). Their concern is increased by the recognition that the study presents only data on an effect level without using other dosages to establish a dose-response relationship and a no-observable-effect level. If such a study had been performed, the resulting no-observable-effect level would have been lower than the 6000 mg/day dosage which produced significant decreases in three reproductive parameters. Thus, the no-effect and exposure levels would be even closer to one another than what is observed now for the effect and exposure levels. The PCRC concludes that (1) DEA-MH produces significant adverse effects on several reproductive parameters and (2) that an ample margin of safety has not been demonstrated as to the reproductive effects produced by DEA-MH. Therefore, the PCRC recommends that a RPAR be triggered for DEA-MH, but not for K-MH. It has been assumed that K-MH would be similar in its action to that of Na-MH.

(3) Conclusion

Even though the PCRC concludes that DEA-MH (but not Na-MH) meets or exceeds the risk criterion for reproductive effects (40 CFR 162.11 (a)(3)(ii)(B), additional data from the registrant is necessary so that the Agency may more precisely estimate the extent of risk caused by the uses of DEA-MH. Consequently, the PCRC and Working Group recommend that affected registrants be required to perform a reproductive study from which dose-response relationships and a no-observable effect level can be determined. In addition, registrants should also be required to submit information on the translocation of DEA-MH to onion bulbs and potato tubers. Further, the PCRC recommends that interested registrants meet with Agency scientists to discuss the adequacy of the protocols developed to meet the above requirements.

IV. Other Studies

This section addresses a study which indicates that DEA-MH may produce an adverse effect but for which insufficient evidence exists to issue a rebuttable presumption. The Working Group recommends that the Agency solicit comment on the evidence presented below and encourage the submission of additional studies or relevant information on this effect.

DEA in MH formulations may react with nitrites and nitrates in plants to form N-nitroso compounds (13). In this study N-nitrosodiethanolamine, a metabolite of DEA, in amounts ranging from 145 to 173 ng/g, has been isolated from tobacco treated with DEA-MH. Cigarette tobacco treated with a mixture of the diethanolamine and potassium salts of MH contained 104 ng of N-nitrosodiethanolamine per gram, whereas a flue-cured tobacco treated only with the potassium salt of MH contained 0.1 ng of N-nitrosodiethanolamine per gram (13). Schmeltz and coworkers (13) in their study referenced the work of Druckrey and coworkers (14) which indicated a finding that N-nitrosodiethanolamine is oncogenic. However, this study is not presently available to enable the Working Group to evaluate the work.

The Working Group therefore unanimously agrees that while they do not have enough information to issue an RPAR on N-nitrosodiethanolamine, the Agency should seek more information related to oncogenicity, to other toxic effects of N-nitrosodiethanolamine and to the potential formation of N-nitrosodiethanolamine in other treated plants and in animals exposed to the diethanolamine salt of MH. Should evaluation of this or any other study that comes to our attention provide an adequate basis for an RPAR, a supplemental Position Document and Federal Register notice will be issued.

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